REMARKS

Applicants have submitted herewith a substitute specification containing tables that comply with the font requirements set forth in 37 C.F.R. § 1.58(c).

Applicants have cancelled Claims 9 and 10 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 1-8 to remove reference to the Figures. Claims 1-6 have been amended to clarify the extracellular domain. Claims 1-5 have been amended to add the limitation that the claimed polypeptides are more highly expressed in normal lung tissue compared to lung tumor, or are encoded by polynucleotide that is more highly expressed in normal lung tissue compared to lung tumor. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendments to Claims 1-5 can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification.

Claims 1-8, and 11-13 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed October 4, 2004. For the reasons set forth below, Applicants respectfully traverse.

Substitute Specification

Applicants submit herewith a substitute specification. The PTO has objected to the original specification, since the font size of the tables does not meet the minimum requirements set forth in 37 C.F.R. § 1.58(c). The formatting of the specification has been corrected and replacement of the current specification with the substitute specification is respectfully requested.

Corrected PTO -1449

Applicants submit herewith a corrected Form PTO -1449. The original form contained a typographical error in the patent number of Jacobs. The number should be 5,536,637, not 5,546,637.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-13 as lacking a specific and substantial, or a well-established utility. One of the asserted utilities for the claimed invention is use as an antigen to make antibodies. However, the PTO asserts that since there is no known physiological or clinical significance of PRO300, and the prior art does not support a very close relationship, (either structural or functional), to a well described family of known proteins, this utility is not substantial or specific. Another asserted utility for the claimed invention is use in drug screening and rational drug design. The PTO has rejected this utility as well, stating that no disease or disorder is known to be associated with the claimed polypeptide. According to the PTO, the use of a polypeptide in drug screening, in the absence of guidance as to what type of disease or disorder the polypeptide causes, or how its involvement could lead to treatment, would require further and undue experimentation. The PTO states that although Example 18 discloses that the polynucleotide is more highly expressed in normal lung as compared to lung tumor tissue, the disclosure gives no guidance as to how to use this information. According to the PTO no levels of expression, relative or absolute, are disclosed. The PTO argues that the information in Example 18 is too sparse to allow the polypeptide to be used as a diagnostic marker. Finally, the PTO states that even if the nucleic acid had utility as a tumor marker, the polypeptide would have no such utility since there is no reason to suspect that the levels of polypeptide vary in normal lung tissue versus lung tumor.

Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that

an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

Applicants have established that the Gene Encoding the PRO300 Polypeptide is Differentially Expressed in Lung Cancer compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed nucleic acids as diagnostic tools, as described in the specification, for example, at paragraph [0337].

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). As Mr. Grimaldi states, "If a difference is detected, this indicates that *the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes*, to screen samples to differentiate between normal and tumor." (Paragraph 7, emphasis added).

The data presented in Example 18 show that the gene encoding PRO300 is more highly expressed in normal lung tissue compared to lung tumor. As the Grimaldi declaration indicates, the disclosed gene and its corresponding polypeptide and antibodies are therefore useful as diagnostic tools. No additional research into how PRO300 is related to cancer is required to use

the disclosed polynucleotides, polypeptides and antibodies to distinguish tumor cells from their normal tissue counterparts. This establishes a substantial utility for the claimed polypeptides.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO argues that even if the nucleic acid has utility as a tumor marker, there is there is no supporting evidence that the polypeptide encoded by the polynucleotide of the instant invention exhibits differential expression in normal lung tissue as compared to lung tumor.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 2). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood

general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (4th ed. 2002) submitted herewith as Exhibit 4). Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Molecular Biology of the Cell at 302, emphasis added. Similarly, figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Molecular Biology of the Cell at 364. This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Molecular Biology of the Cell at 379.

Together, the declarations of Mr. Grimaldi and Dr. Polakis and the cited textbook establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO300 mRNA is expressed at a higher level in normal lung tissue compared to lung tumor the PRO300 polypeptide will also be expressed at a higher level in normal lung tissue compared to lung tumor. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as a diagnostic tool. As the PTO has acknowledged, "if the protein has utility, then this confers utility upon the polynucleotide...." Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the PRO300 polypeptide, and the nucleic acids which encode it, as a cancer diagnostic tool.

Applicants submit that they have therefore established two separate bases for utility of the claimed polypeptides. The first argument is based on the differential expression of the PRO300 encoding gene in normal lung tissue compared to lung tumor. The second argument is based on

the utility of the PRO300 polypeptides as diagnostic tools, given that it is well-established in the art that there is a correlation between gene expression and protein expression.

The Claimed Polypeptides would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Expression of the Encoded Polypeptide

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO300, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 5), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 6). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in

cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed polypeptides.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that there is no known physiological or clinical significance of PRO300, or disease or condition disclosed as being associated with PRO300. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO300 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the polypeptides.

As discussed above, there are significant data that show that the gene encoding the PRO300 polypeptide is more highly expressed in normal lung tissue compared to lung tumor. These data are strong evidence that the gene encoding the PRO300 polypeptide is associated with lung tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the gene encoding PRO300 with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly lung tumor, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has asserted various arguments why the claimed polynucleotides lack substantial utility: (1) there is no known physiological or clinical significance of PRO300; (2) there is no known disease or disorder associated with PRO300, or guidance as to how PRO300 could lead to a treatment; (3) there is no guidance as to how information regarding how differential gene expression levels can be used; (4) there is no disclosure regarding absolute or relative levels of expression of the gene encoding PRO300 in normal lung compared to lung tumor; and (5) that differential expression of the claimed nucleic acids does not necessarily correlate with differential expression of the encoded polypeptides. Applicants have addressed each of these arguments in turn.

First, Applicants have pointed out that the data in Example 18 establish a physiological and clinical significance for PRO300 because the gene encoding PRO300 is differentially expressed in lung cancer cells compared to normal lung tissue. The data in Example 18 provide strong evidence that PRO300 is associated with lung tumors.

Applicants have provided a declaration stating that given the relative difference in expression levels the claimed nucleic acids have utility as cancer diagnostic tools. The fact that the levels of expression of the gene encoding PRO300 are different in normal lung tissue versus lung tumor provides the bases for the utility of the claimed polypeptides. This is not a general utility that would apply to the broad class of polypeptides.

Applicants have also provided a declaration stating that the data in Example 18 reporting higher expression of the PRO300 gene in normal lung compared to lung tumor are real and significant.

Finally, Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the PRO300 polypeptide has utility as a diagnostic tool for cancer.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is <u>not</u> required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides relating to PRO300 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejection of Claims 1-5, 12 and 13 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the claims do not require that the claimed polypeptides possess any particular biological activity, particular conserved structure, or other disclosed distinguishing feature, the claims fail the written description requirement. The PTO states that the only factor present in the claims is a partial structure in the form of a recitation of percent identity. The PTO concludes that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The PTO also states that the specification does not describe the extracellular domain of the polypeptide of SEQ ID NO: 12, since there is no information as to whether the polypeptide is transported to/through the cell's membrane. Finally, the PTO states that because the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, conception is not achieved until reduction to practice has occurred.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc.*

v. Mahurkar, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The instant invention, defined by the amended claims, concerns polypeptides having a specified sequence identity with the specified polypeptide sequence of SEQ ID NO: 12, and as amended, with the functional recitation: "wherein said isolated polypeptide is more highly expressed in normal lung tissue compared to lung tumor, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal lung tissue compared to lung tumor". Based on the detailed description of the cloning and expression of variants of PRO300 in the specification, the description of the gene expression assay, the actual reduction to practice of sequences SEQ ID NOs: 11 and 12, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the invention as claimed in the instant claims.

Figure 12 describes the polypeptide of SEQ ID NO: 12, and indicates the precise location of ten transmembrane domains and a signal sequence within the polypeptide. A skilled artisan would readily appreciate that the Applicants were in possession of the invention, including the extracellular domains, at the time of the disclosure given the information provided in Figure 12.

At the time of the disclosure, those of skill in the art recognized that signal sequences target membrane-spanning (i.e., containing at least one extracellular domain) and secreted proteins to the rough endoplasmic reticulum such that they are ultimately correctly localized. See, Alberts et al., *Molecular Biology of the Cell* (1983), Grand Publishing Co., pp. 341-345, submitted as Exhibit 7. Thus, Claims 1-6, which claim the extracellular domain of the polypeptide of SEQ ID NO: 12, are adequately described in Figure 12.

Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-6, 9 and 12-13 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase "the extracellular domain" as no extracellular domain for PRO3000 is identified.

Applicants respectfully submit that the pending claims are not indefinite as both the extracellular domains and the signal peptide regions are well-defined in Figure 12, which precisely defines the amino acid residues of SEQ ID NO: 12 that span the membrane, as well as the amino acid residues that constitute the signal sequence. Applicants have amended Claims 1-6 to further clarify the extracellular domains.

Rejection under 35 U.S.C. §102(b) – Anticipation

The PTO rejects Claims 1-6 as anticipated under 35 U.S.C. § 102(b) by WO 01/16318 to Eaton *et al.*, published in March 2001. Presumably, this rejection is based on the PTO's determination that the disclosure to which priority is claimed fails to meet the requirements of §§101 and 112, first paragraph, and thus setting the priority at the instant filing date, May 1, 2002. The PTO asserts that WO 01/16318 teaches the polypeptide of SEQ ID NO: 12, which is 100% identical to SEQ ID NO: 12 of the instant application, as well as chimeric molecules comprising SEQ ID NO: 12 fused to an epitope tag or an Fc region of an immunoglobulin.

To anticipate under 35 U.S.C. § 102(b), the invention must be patented or described in a printed publication "more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). Under 35 U.S.C. § 120, an applicant is entitled to the benefit of the filing date of an earlier filed application that discloses the same invention in the manner provided by 35 U.S.C. § 112, first paragraph, provided that the applicant properly claims

priority to the earlier application. In a preliminary amendment filed on September 3, 2002, Applicants made specific reference to WO 01/16318, claiming priority thereto. WO 01/16318 contains the same disclosure regarding PRO300 and its utilities as the instant application, including the data in Example 18. For the same reasons detailed above in the Remarks addressed to the rejections under 35 U.S.C. §§ 101 and 112 in the instant response, Applicants submit that WO 01/16318 is enabling for the claimed invention. Therefore, because Applicants have properly claimed priority to WO 01/16318, and because WO 01/16318 satisfies the requirements of 35 U.S.C. § 112, Applicants are fully entitled to the benefit of the filing date of WO 01/16318. Thus, Applicants respectfully request that the PTO reconsider and withdraw the rejection under 35 U.S.C. § 102(b).

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Jan. 3, 2005

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